



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: <b>PCT/CA99/01058</b>		(74) Agents: DUBUC, Jean, H. et al.; Goudreau Gage Dubuc & Martineau Walker, The Stock Exchange Tower, Suite 3400, 800 Place Victoria, Montreal, Quebec H4Z 1E9 (CA).																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																										
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## (57) Abstract

Using RT-PCR and degenerate oligonucleotides derived from the active site residues of subtilisin-kexin-like serine proteinases, we have identified a highly conserved and phylogenetically ancestral human, rat and mouse type-I membrane-bound proteinase called subtilisin-kexin-isozyme-1 (SKI-1). Computer data bank searches reveals that human SKI-1 was previously cloned but with no identified function. A SKI-1 processed fragment is secreted in culture media in a soluble form. *In vitro* studies suggest that SKI-1 is a  $\text{Ca}^{2+}$ -dependent serine proteinase exhibiting a wide pH optimum for cleavage of proBDNF. Peptides mimicking SKI-1 cleavage sites are also disclosed. SKI-1 prosegment has an *ex vivo* inhibitory effect on SKI-1 activity. The prosegment is also processed and secreted in culture media. One of its fragments is found tightly associated with the SKI-1 soluble form. Therapeutic applications for SKI-1 inhibitors are disclosed.